

Evaluation of serum ferritin as a marker for adult Still's disease activity

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Abstract

Extremely high serum ferritin values ($>10\,000\ \mu\text{g/l}$) were detected in two patients with adult Still's disease. The ferritin concentrations decreased to normal after adequate treatment. During a one year follow up ferritin concentration was helpful in monitoring disease activity and guiding decisions about treatment. Raised concentrations of soluble interleukin 2 receptors (sCD25) were also found. Detection of ferritin values above $3000\ \mu\text{g/l}$ should lead to the consideration of Still's disease when there is an acute febrile illness without evidence for bacterial or viral infections, serum ferritin being suitable for monitoring treatment.

Still's disease is an acute systemic inflammatory illness that was first described in children but rarely also affects adults.^{1,2} Although fever, arthralgias/arthritis, myalgia, skin rash, lymphadenopathy, and sore throat are present in most patients,³ there are no pathognomonic symptoms or laboratory abnormalities for this disease and its incidence is probably underestimated, particularly in adults. A large number of diagnostic procedures are usually performed before diagnosis is made, and empirical treatment, particularly antibiotic, is often started in the assumption of an infectious disease. As a result, diagnosis and adequate treatment are usually delayed.

Among the typical features of Still's disease are increased laboratory inflammatory parameters; in one study abnormally high serum ferritin values were reported in 20 children with Still's disease,⁴ and it was suggested that high ferritin levels may be a diagnostic marker of Still's disease.⁵ In this report we present two cases of adult Still's disease that were characterised by extremely high serum ferritin values. A one year follow up is reported: the changes in serum ferritin noted after adequate treatment underline the usefulness of this marker for Still's disease, and suggest that ferritin can be used both as a diagnostic help and for guiding decisions about treatment.

Case reports

PATIENT 1

A 29 year old woman presented in February 1990 with temperature spikes up to 40°C , arthritis of several small and large joints, severe myalgia, and sore throat. A mildly pruritic rash was seen on the trunk and the extremities on admission. Abnormal laboratory values included

normocytic anaemia with haemoglobin of $83\ \text{g/l}$, a neutrophilic leucocytosis of 13.8×10^9 white blood cells/l, with 13% juvenile forms in the differential count, an erythrocyte sedimentation rate (ESR) of $71\ \text{mm/h}$, C reactive protein (CRP) $262\ \text{mg/l}$ (normal $<8\ \text{mg/l}$). Serum lactate dehydrogenase was $909\ \text{IU/l}$ ($15.15\ \mu\text{kat/l}$) (normal up to $240\ \text{U/ml}$), serum iron was reduced to $4\ \mu\text{mol/l}$, serum ferritin was extremely high with a value of $12\,406\ \mu\text{g/l}$ (normal $20\text{--}300\ \mu\text{g/l}$). Also, the soluble interleukin 2 receptor (sCD25) showed a striking increase up to $3200\ \text{U/ml}$ (normal $<930\ \text{U/ml}$ (enzyme linked

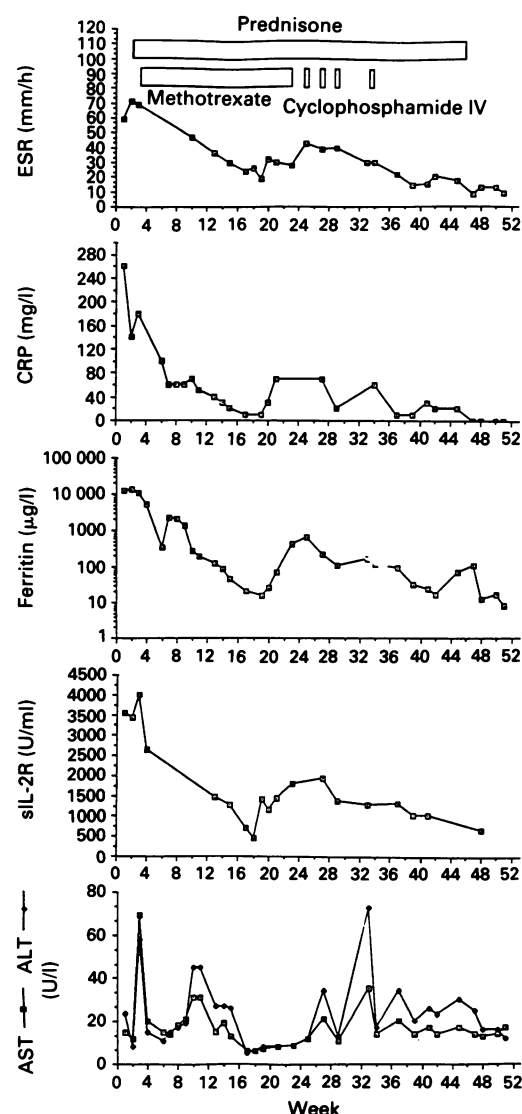


Figure 1 Change in erythrocyte sedimentation rate (ESR), C reactive protein (CRP), ferritin, soluble interleukin 2 receptor (sIL-2R), and aspartate transaminase/alanine transaminase (AST/ALT) during treatment of patient No 1.

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immunosorbent assay (ELISA; T cell Science, NC, USA)). Liver enzymes were only slightly raised, as were α_1 and α_2 globulins; several other parameters, including rheumatoid factor, antinuclear antibodies, complement concentrations, antibodies to several bacterial, fungal, and viral antigens were normal. Blood, urine, and stool cultures were also repeatedly negative. Based on the clinical findings and the lack of evidence for an infectious cause, adult onset Still's disease was diagnosed, and treatment with high dosage salicylates, non-steroidal anti-inflammatory agents, and corticosteroids was started. Despite aspirin doses up to 6 g/day and prednisolone doses up to 300 mg/day symptoms improved only partially, and immunosuppressive therapy with methotrexate 40 mg intravenously once weekly was begun. After eight weeks symptoms had resolved and laboratory values had largely returned to normal. Besides ESR and CRP the soluble interleukin 2 receptor and serum ferritin also showed a dramatic decrease (fig 1). Upon methotrexate reduction (10 mg once weekly orally) symptoms recurred (sore throat, arthralgia, skin rash) and laboratory

inflammatory values began to rise again. Monthly intravenous pulse therapy with cyclophosphamide, 1 g/dose was started, and after four courses of treatment remission of both symptoms and laboratory changes was achieved. Remission is currently maintained with aspirin 4 g/day and prednisone 10 mg/day.

PATIENT 2

A 21 year old man presented with fever up to 39°C, myalgia, arthralgia, weight loss (13 kg in 4 weeks), and sore throat. A skin rash could not be detected on admission but was reported in the preceding days. Abnormal laboratory test values included normocytic anaemia of 95 g/l, slight neutrophilic leucocytosis of 13.9×10^9 white blood cells/l, an ESR of 93 mm/h, C reactive protein 10.4 mg/l, lactate dehydrogenase 580 IU/ml, serum iron 2 $\mu\text{mol/l}$, serum aspartate transaminase 90 IU/l (1.50 $\mu\text{kat/l}$), serum alanine transaminase 94 IU/l (1.56 $\mu\text{kat/l}$), γ -glutamyltransferase 70 IU/l (1.16 $\mu\text{kat/l}$). Serum ferritin was 13 300 $\mu\text{g/l}$ and in the first days after admission it rose up to a maximum of 23 727 $\mu\text{g/l}$. Treatment was started with aspirin 1 g/day, leading to an improvement but not to a resolution of the symptoms, so that corticosteroid treatment was started. Complete recovery occurred after four weeks (fig 2), and the patient is at present still in remission.

Discussion

Owing to the lack of pathognomonic symptoms and laboratory abnormalities, diagnosis of Still's disease is often difficult to establish, particularly when the disease occurs in adult life. It frequently is an exclusion diagnosis, which implies in many cases both a large number of needless investigations and a considerable delay in starting adequate treatment. Our report indicates that serum ferritin concentration can be used as a valuable marker, both as a diagnostic tool and as a treatment guideline for adult Still's disease.

The conditions in which serum ferritin has been reported to be markedly raised include malignancies, such as acute and chronic leukaemias, malignant lymphomas, melanoma, neuroblastoma and germ cell tumours, acute liver necrosis, and haemochromatosis (mostly conditions usually suggested by other clinical or laboratory findings).⁶⁻⁸ Even in these conditions, however, serum ferritin concentrations rarely exceed values of 3000 $\mu\text{g/l}$ and values above 5000 $\mu\text{g/l}$ are extremely unusual. Besides being an important diagnostic tool, serum ferritin appears to be a reliable marker for monitoring disease activity and for guiding decisions about treatment, as exemplified by the one year follow up of our two patients. Certainly, ESR, CRP, and the soluble interleukin 2 receptor, which are greatly increased in active disease, can be used to assess disease activity, but the likelihood that these parameters are raised owing to intercurrent diseases is much higher than for ferritin. This may be clinically relevant particularly in patients receiving immunosuppressive therapy, as our patient 1.

Recently, raised serum ferritin concentrations

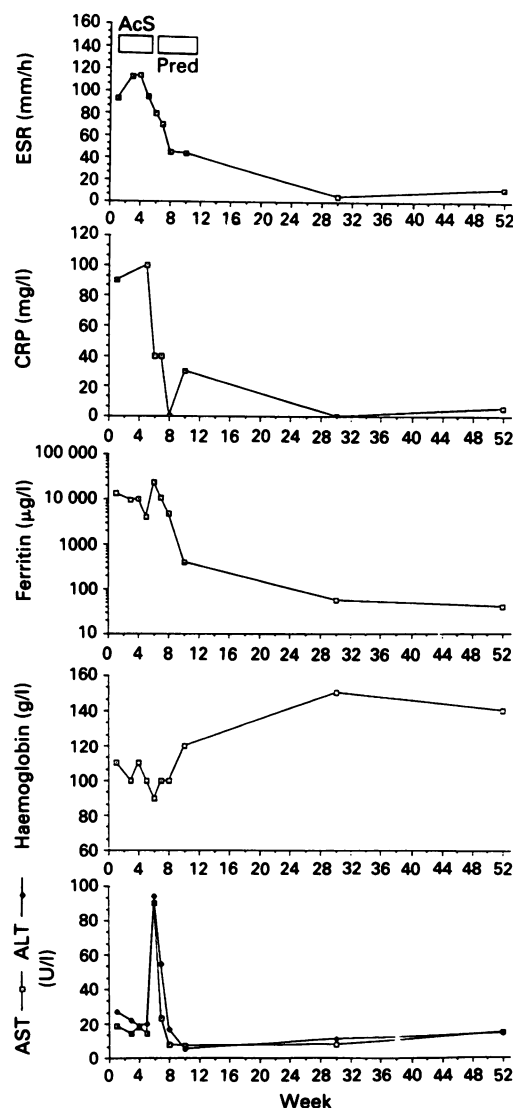


Figure 2 Change in erythrocyte sedimentation rate (ESR) C reactive protein (CRP), ferritin, haemoglobin, and aspartate transaminase/alanine transaminase (AST/ALT) during treatment of patient No 2.

have been reported in 20 children with Still's disease⁴ and two diagnoses of Still's disease were reported in patients with a series of serum samples with raised serum ferritin concentrations.⁵

The origin of the extremely high ferritin concentrations in Still's disease remains unclear. As high ferritin concentrations can be found in liver cell necrosis it is possible that in Still's disease liver damage may be responsible for the release of this protein in the serum; however, both the liver enzyme increase found in the disease and the transaminase curve of patient 1 during treatment (which does not strictly correlate with the ferritin curve) argue strongly against this possibility. Interesting clues that may help to clarify the pathogenesis of this intriguing disease come from recent observations that interleukin 1 β may induce increased synthesis of ferritin by increasing the association of ferritin mRNA with polyribosomes in human hepatoma cells.⁹ This enhancement of ferritin mRNA translation is not related to the iron dependent regulation of ferritin synthesis. Similar findings were obtained using heat-shock avian reticulocytes.¹⁰ So, an iron regulated pathway of enhanced ferritin synthesis may cause the moderately raised ferritin-concentrations found in haemochromatosis or related conditions, whereas direct activation

through cytokines may be responsible for the extremely high ferritin concentrations that seem to be associated with Still's disease. In this respect it is interesting to note that our patient No 1 also had raised levels of soluble interleukin 2 receptor. Thus raised cytokine activity in Still's disease may be responsible for both clinical and laboratory findings. This is a testable hypothesis that may provide new clues to the pathogenesis of this intriguing disease.

- 1 Still G. On a form of chronic joint disease in children. *Med Chir Trans* 1897; **80**: 47.
- 2 Bywaters E G L. Still's disease in the adult. *Ann Rheum Dis* 1971; **30**: 121-33.
- 3 Ohta A, Yamaguchi M, Kaneoka H, Nagayoshi T, Hiida M. Adult Still's disease: review of 228 cases from the literature. *J Rheumatol* 1987; **14**: 1139-45.
- 4 Pelkonen P, Swanljung K, Siimes M A. Ferritinemia as an indicator of systemic disease activity in children with systemic juvenile rheumatoid arthritis. *Acta Paediatr Scand* 1986; **75**: 64-8.
- 5 Gonzalez-Hernandez T, Martin-Mola E, Fernandez-Zamoeano A, Balsa-Criado A, de Miguel-Mendieta E. Serum ferritin can be useful for diagnosis in adult onset Still's disease. *J Rheumatol* 1989; **16**: 412-3.
- 6 Mirahmadi K S, Paul W L, Winer R L, *et al.* Serum ferritin levels. *JAMA* 1977; **238**: 601-3.
- 7 Worwood M. Serum ferritin. *Clin Sci* 1986; **70**: 215-20.
- 8 Prieto J, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver diseases. *Gastroenterology* 1965; **68**: 526-33.
- 9 Rogers J T, Bridges K R, Durmowicz G P, Glass J, Auron P E, Munro H N. Translational control during the acute phase response. Ferritin synthesis in response to interleukin-1. *J Biol Chem* 1990; **265**: 14572-8.
- 10 Atkinson B G, Blaker T W, Tomlinson J, Dean R L. Ferritin is a translationally regulated heat shock protein of avian reticulocytes. *J Biol Chem* 1990; **265**: 14156-62.